Average daily ischemic versus bleeding risk in patients with ACS undergoing PCI: Insights from the BleeMACS and RENAMI registries

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Background
The risk of recurrent ischemia and bleeding after percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) may vary during the first year of follow-up according to clinical presentation, and medical and interventional strategies.
Methods
BleeMACS and RENAMI are 2 multicenter registries enrolling patients with ACS treated with PCI and clopidogrel, prasugrel, or ticagrelor. The average daily ischemic and bleeding risks (ADIR and ADBR) in the first year after PCI were the primary end points. The difference between ADBR and ADIR was calculated to estimate the potential excess of bleeding/ischemic events in a given period or specific subgroup.
Results
A total of 19,826 patients were included. Overall, in the first year after PCI, the ADBR was 0.008085%, whereas ADIR was 0.008017% (*P* = .886). In the first 2 weeks ADIR was higher than ADBR (*P* = .013), especially in patients with ST-segment elevation myocardial infarction or incomplete revascularization. ADIR continued to be, albeit non-significantly, greater than ADBR up to the third month, whereas ADBR became higher, although not significantly, afterward. Patients with incomplete revascularization had an excess in ischemic risk (*P* = .003), whereas non–ST-segment elevation ACS patients and those on ticagrelor had an excess of bleeding (*P* = .012 and *P* = .022, respectively).
Conclusions
In unselected ACS patients, ADIR and ADBR occurred at similar rates within 1 year after PCI. ADIR was greater than ADBR in the first 2 weeks, especially in ST-segment elevation myocardial infarction patients and those with incomplete revascularization. In the first year, ADIR was higher than ADBR in patients with incomplete revascularization, whereas ADBR was higher in non–ST-segment elevation ACS patients and in those discharged on ticagrelor.

Patients with acute coronary syndromes (ACS) treated with percutaneous coronary intervention (PCI) have a substantial rate of recurrent ischemic and bleeding adverse events, in part due to the increased life expectancy which has raised the median age of patients presenting with ACS. Older patients present a larger rate of comorbidities such as malignancy, frailty, and chronic kidney disease (CKD) which increase both the ischemic and the hemorragic risk.[1, 2] Conversely, technological improvements support the obtainment of satisfactory results with PCI even in challenging anatomies, although prolonged dual antiplatelet therapy (DAPT) is often required.[3-7] Choosing among clopidogrel, prasugrel, and ticagrelor treatments and related durations may depend on the relative ischemic and bleeding risks.[8-10]
Recently, Giustino et al reported the average daily ischemic risk (ADIR) and average daily bleeding risk (ADBR) in different time intervals after PCI among patients with ST-segment elevation myocardial infarction (STEMI) who were enrolled in the HORIZONS-AMI trial, showing a greater risk of bleeding within the first 30 days and a greater risk of ischemia between 30 days and 1 year.[11] This study, however, was limited by strict inclusion criteria (only patients with STEMI) and exclusion of some high-risk patients, such as those with previous stroke or bleeding.[11,12] Consequently, we reviewed the ADIR and ADBR in 2 large contemporary cohorts of ACS patients treated with clopidogrel, prasugrel and ticagrelor, with the aim of understanding the absolute and relative adverse events rates in a real-life population.[13,14]

Methods

The study population was selected from the REgistry of New Antiplatelets in patients with Myocardial Infarction (RENAMI) and Bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome (BleeMACS) registries, with a total of 19,826 patients with ACS undergoing PCI analyzed.
RENAMI included 4424 patients aged ≥18 years with STEMI and non-STEMI who underwent coronary angiography and PCI and were treated with DAPT using aspirin and ticagrelor, prasugrel, or clopidogrel. RENAMI patients were enrolled from 12 European centers between 2012 and 2016.[14]
BleeMACS is an international multicenter investigator-initiated retrospective registry comprised of 15,402 consecutive patients discharged alive after admission for ACS and treated with PCI during the index admission. Patients in the BleeMACS registry were enrolled from 15 tertiary hospitals in Europe, Asia, and North and South America between 2003 and 2014.[13] Both registries had no exclusion criteria. The institutional review board of each center approved participation in the BleeMACS and RENAMI registries.

Clinical data and follow-up

Clinical data (eg, cardiovascular risk factors, clinical presentation), interventional data (eg, access, extent of coronary disease, and treatment), and outcomes were collected by a trained study coordinator in each center. Clinical assessments, ECG recordings, and further examinations (when required) were performed periodically in every patient with recording of the exact date of recurrent events.

Definition and end points

Bleedings events were defined as type 2-5 according to the Bleeding Academic Research Consortium definition.[15] Ischemic events were defined as myocardial infarction (MI) and definite stent thrombosis (ST). Incomplete revascularization was defined as the presence of a residual stenosis ≥70% in a non–left main coronary artery or stenosis ≥50% in the left main after PCI.
The ADIR and ADBR in the first year after PCI for ACS were the primary end points. The difference between average daily bleeding and ischemic risk was calculated to detect the presence of a potential excess of bleeding/ischemic events in a given period or in a specific subgroup (sex; elderly people ≥75 years old; type of P2Y12 inhibitor among clopidogrel, prasugrel, and ticagrelor; type of infarction [ST-segment Elevation (STE) vs Non ST-segment Elevation (NSTE) ACS], completeness of revascularization, and history of malignancy). Instantaneous daily bleeding and ischemic rates were calculated dividing the number of events occurring in a specific day post-PCI for ACS by the number of exposed people on the same day. As the registries analyzed in this study take into consideration only single events, patients who had an event were excluded from the population at risk thereafter. The average risks were defined as the total number of events in that specific time interval divided by the total number of patient-days of follow-up, that is, the total number minus loss at follow-up, deaths, and people who already had an event. After calculation of daily risks, paired *t* test was applied to verify if there was a significant difference in term of ischemia/bleeding during the various time frames and subgroups. Statistical significance was defined as *P* value < .05.
No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, and the drafting and editing of the paper.

Results

A total of 19,826 total patients with ACS were included. The average age of the patients was 63 ± 12.5 years, 23% were female, and 25% had diabetes mellitus. Patients presenting with STEMI were 11,506 (58%), 2,366 (12%) were treated with prasugrel, and 3,356 (17%) were treated with ticagrelor (Table I).

Average ischemic and bleeding risk in the first year

There were 563 ischemic events and 567 bleeding events in our population in the first year of follow-up. ADBR and ADIR trends over time are shown in Figure 1. The ADBR in the first year was 0.008085%; the ADIR was 0.008017% (ADIR-ADBR = 0.000068%, *P* = .88). The same results were observed in all the subgroups, except those with incomplete revascularization (Table II and Figure 2), in whom an excess in ischemic risk was noted (ADIR-ADBR = 0.003264881%, *P* = .003), and NSTE-ACS patients and those taking ticagrelor, who showed an excess of daily bleeding risk (ADIR-ADBR = −0.001725756%, *P* = .012 for NSTE-ACS; and ADIR-ADBR = −0.002356313%, *P* = .022 for ticagrelor use). There was no significant difference in the time distribution of bleeding risk in patients with NSTE-ACS and in ticagrelor patients compared with the overall population.

Average ischemic and bleeding risk in the first month

In the acute phase (≤24 hours), the ADIR was 0.0605357% and the ADBR was 0.025223%, with an ADIR-ADBR = 0.0353127. In the first week, there was a significantly higher ischemic risk compared to bleeding (ADIR-ADBR = 0.015170%, *P* = .048) due to an excess of ischemic events in the subgroups of patients with incomplete revascularization (ADIR-ADBR = 0.043110%, *P* = .018) and male patients (ADIR-ADBR = 0.023384%, *P* = .024). In the first 2 weeks after ACS, in the entire population, ischemic risk was higher than bleeding risk (ADIR-ADBR = 0.011220%, *P* = .013) due to an excess of ischemic events in patients with incomplete revascularization (ADIR-ADBR = 0.029703%, *P* = .005) and males (ADIR-ADBR = 0.013108%, *P* = .033), but also in patients who were hospitalized for STEMI (ADIR-ADBR = 0.018098%, *P* = .02) and patients taking clopidogrel (ADIR-ADBR = 0.013740%, *P* = .026). This difference was no longer significant in the entire population when comparing risks in the first month (ADIR-ADBR = 0.004909%, *P* = .066) but persisted in those with STEMI (ADIR-ADBR = 0.010520%, *P* = .020) and incomplete revascularization (ADIR-ADBR = 0.018372%, *P* = .004) subgroups (Table III and Figure 3).

Average ischemic and bleeding risk from 2 to 12 months

After the first month, the rates of ADIR and ADBR in the overall population were essentially superimposable, without significant difference. ADIR tended to be greater than ADBR during the second and third months, whereas ADBR occurred more frequently, although not significantly, from the fourth to the 12th months (Table IV and Figure 4).

Discussion

The analysis from this large-scale population of patients with ACS undergoing PCI highlighted the following: (1) an overall low risk of both ischemic and bleeding complications within the first year; (2) a significant excess of daily ischemic risk detected during the first 2 weeks, more pronounced in patients with STEMI, those with incomplete revascularization, and patients taking clopidogrel as P2Y12 inhibitor; (3) declining trends toward greater ischemic risk for the first 3 months, whereas the bleeding risk demonstrated a nonsignificant trend to predominance after the fourth month; (4) patients with incomplete revascularization presented significantly higher ADIR, whereas patients treated with ticagrelor and those with NSTE-ACS presented higher ADBR throughout the whole year.

Optimizing the balance between ischemic and bleeding risk still represents challenge for physicians managing ACS patients with PCI. In a recent subanalysis from the ACUITY trial,[16] recurrent MI was directly linked to mortality, especially for ischemic events occurring within 30 days after the index PCI. Conversely, major bleeding in the same cohort was associated with increased mortality throughout the 1-year follow up.

In the present analysis of recurrent ischemic and bleeding risks after PCI in ACS in more than 19,000 patients, the ADIR was greater than ADBR in the first 2 weeks, especially in STEMI patients and in those with incomplete revascularization or in those treated with clopidogrel. In contrast, Giustino et al[11] reported that in the large randomized HORIZONS-AMI of patients with STEMI treated with clopidogrel, both ADIR and ADBR were highest in the first 24 hours after primary PCI and then declined rapidly. In that study, the rates of ADIR and

ADBR were similar in the first 24 hours; ADBR was greater than ADIR between 1 and 30 days; and then ADIR was greater than ADBR between 1 and 12 months. The discrepancy of our results from this report may in part reflect differences in patients and types of ADP antagonists used. In-hospital mortality of STEMI patients is higher than NSTE-ACS (not included in HORIZONS-AMI but representing 42% of our patients), and comorbidities were more commonly present in our unselected patient population.[16] Moreover, one third of our population received ticagrelor or prasugrel which, compared to treatment with clopidogrel, has been shown to reduce ischemic events particularly in the first 30 days at the cost of a constant increase in non–CABG-related bleeding through the first year.[17-20] The definition of AIDR and ADBR differed somewhat between HORIZONS-AMI and the present study. Specifically, cardiac death was considered a component of ADIR in HORIZONS-AMI but not in our study, and ADBR was defined as Thrombolysis in Myocardial Infarction major or minor bleeding in HORIZONS-AMI versus Bleeding Academic Research Consortium types 2-5 in the present study. Giustino counted all events, whereas in our study, patients were censored after the first event. Finally, we cannot exclude differences in the sensitivity or accuracy of adverse event ascertainment between a randomized trial and large registries.

In the present analysis, a declining trend of ischemic risk was noted after the first month, and an increased trend of bleeding after the fourth month was observed. This held true for STEMI and NSTE-ACS patients. These data support the findings from the TOPIC trial,[21] suggesting that deescalating DAPT potency to clopidogrel after 3 months versus continued use of prasugrel or ticagrelor may provide a net favorable balance of ischemia versus bleeding - of course, this should not be a one-size-fits-all strategy but shall be tailored on each patient. Of note, the results of the analysis differ among specific patient cohorts including those with NSTE-ACS, incomplete revascularization, and ticagrelor use. Complete revascularization in both STEMI and NSTE-ACS has been associated with improved event-free survival.[22-25] and with reductions in both mortality and recurrent ischemic events. In large registries,[22,26] complete revascularization has been achieved in less than half of the patients, resulting in increased ischemia due to disease progression and thrombosis of nonculprit lesions.[27,28] The present findings suggest that potent P2Y12 inhibitors may be of particular benefit if complete revascularization is not achieved. Similarly, the increased bleeding risk in NSTE-ACS patients is related to comorbidities including renal insufficiency or malignancy.[16] The excess of bleeding risk on ticagrelor, most evident after the first 3 months[17,19,20] and not described for prasugrel, is perhaps related to contraindication in patients >75 years old, <60 kg in weight, and with previous stroke for the latter, all of which have been associated with major bleeding.

Limitations could affect the generality of our findings. As mentioned previously, patients were censored after occurrence of the first event; we did not consider the relationship between sequential ischemic and bleeding events. However, analysis of the first event provides clinically relevant insights because medical therapy is often individually tailored after the first bleeding or ischemic event. The attributable risks of ischemic and bleeding events to subsequent mortality were not determined in our analysis, which would be helpful to weight the relative risks of each and the benefits of their prevention. A further limitation is the lack of randomization, introducing the risk for both overt and unmeasured confounders (eg, relevant to the analysis of the outcomes after the different P2Y12 inhibitors). Finally, no data regarding adherence to DAPT were available.

Conclusions

In a large series of unselected ACS patients treated with PCI, ADIR was more prevalent than ADBR in the first 2 weeks, especially in patients with STEMI and incomplete revascularization. In the first year, ADIR was higher than ADBR only in patients with incomplete revascularization. Patients with NSTE-ACS and those discharged with ticagrelor had higher ADBR. These data emphasize the importance of considering the type of ACS presentation, the completeness of revascularization by PCI, and the potency of the prescribed P2Y12 inhibitor used as part of a DAPT regimen to optimize the risks of bleeding and ischemia after PCI.

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Table I. Baseline features of included patients

Age, y	63 ± 12.5
Female sex, n (%)	4514 (22.8)
Diabetes mellitus, n (%)	5023 (25.3)
Hypertension, n (%)	11,426 (57.6)
CKD, serum creatinine >2 mg/dL, n (%)	916 (4.6)
Prior ACS, n (%)	2571 (13.0)
Prior PCI, n (%)	2715 (13.7)
Prior coronary artery bypass graft, n (%)	549 (2.8)
Prior stroke, n (%)	1136 (5.7)
Peripheral vascular disease, n (%)	998 (5.0)
Prior bleeding, n (%)	908 (4.6)
STEMI, n (%)	11,506 (58.0)
NSTE-ACS, n (%)	8319 (42.0)
Malignancy, n (%)	1126 (5.7)
Complete revascularization, n (%)	9667 (48.8)
Prasugrel, n (%)	2366 (11.9)
Ticagrelor, n (%)	3356 (16.9)
Clopidogrel, n (%)	14,105 (71.1)
Oral anticoagulants, n (%)	839 (4.2)

Table II. Average ischemic and bleeding risk in first year

	Mean difference (%)	95% CI		*P* value
ADIR-ADBR	−0.000067704	−0.00099724	0.000861835	.886
ADIR-ADBR ≥75 y	−0.001006011	−0.00399206	0.001980043	.508
ADIR-ADBR prasugrel	−0.000472744	−0.00235484	0.001409354	.622
ADIR-ADBR ticagrelor	−0.002356313	−0.00437495	−0.00033768	.022
ADIR-ADBR clopidogrel	0.000537171	−0.00065758	0.001731925	.377
ADIR-ADBR STEMI	0.001160846	−0.00018196	0.002503654	.090
ADIR-ADBR NSTE-ACS	−0.001725756	−0.00306783	−0.00038368	.012
ADIR-ADBR complete revascularization	−0.000124015	−0.00141543	0.001167401	.85
ADIR-ADBR incomplete revascularization	0.003264881	0.001088246	0.005441517	.003
ADIR-ADBR malignancy	0.001111956	−0.0049406	0.007164511	.718
ADIR-ADBR female	−0.000660302	−0.00288753	0.001566927	.560
ADIR-ADBR male	0.000120371	−0.0009287	0.001169438	.822

Table III. Average ischemic and bleeding risk in the first month.

Empty Cell	ADIR-ADBR	Mean	CI		*P* value
	Overall	**0.015170173**	**0.000158414**	**0.030181932**	**.048**
First week	**Incomplete**	**0.043110144**	**0.010204361**	**0.076015927**	**.018**
	Male	**0.023384492**	**0.00430895**	**0.042460033**	**.024**
	Overall	**0.01121985**	**0.002790391**	**0.019649309**	**.013**
	Clopidogrel	**0.013740296**	**0.001959429**	**0.025521163**	**.026**
First and second week	**STEMI**	**0.01809808**	**0.003270249**	**0.032925912**	**.021**
	Incomplete	**0.029703444**	**0.010746961**	**0.048659927**	**.005**
	Male	**0.013107857**	**0.001248635**	**0.024967079**	**.033**
	Overall	**0.004909367**	**−0.00033823**	**0.010156963**	**.660**
First month	**STEMI**	**0.010519860**	**0.00181001**	**0.019229621**	**.020**
	Incomplete	**0.018372411**	**0.006426152**	**0.030318670**	**.004**

Table IV. Average ischemic and bleeding risk from months 2 to 12

Empty Cell	ADIR-ADBR	Mean	CI		*P* value
2nd month	Overall	0.001554626	−0.001663114	0.004772365	.331
3rd month	Overall	0.002597388	−0.000503847	0.005698624	.097
4th month	Overall	−0.002222454	−0.005874278	0.001429370	.223
5th month	Overall	−0.005368086	−0.010009198	−0.000726975	.025
6th month	Overall	−0.001048352	−0.003888229	0.001791526	.456
7th month	Overall	0.000528290	−0.002716475	0.003773054	.742
8th month	Overall	0.000531657	−0.002325651	0.003388965	.706
9th month	Overall	−0.001590360	−0.003746537	0.000565817	.142
10th month	Overall	0.000533078	−0.001763037	0.002829193	.638
11th month	Overall	−0.001247448	−0.003686492	0.001191596	.304
12th month	Overall	-0.000001240	-0.002278743	0.002276263	.999

Figure 1. Daily ADIR and ADBR in the first year, overall.

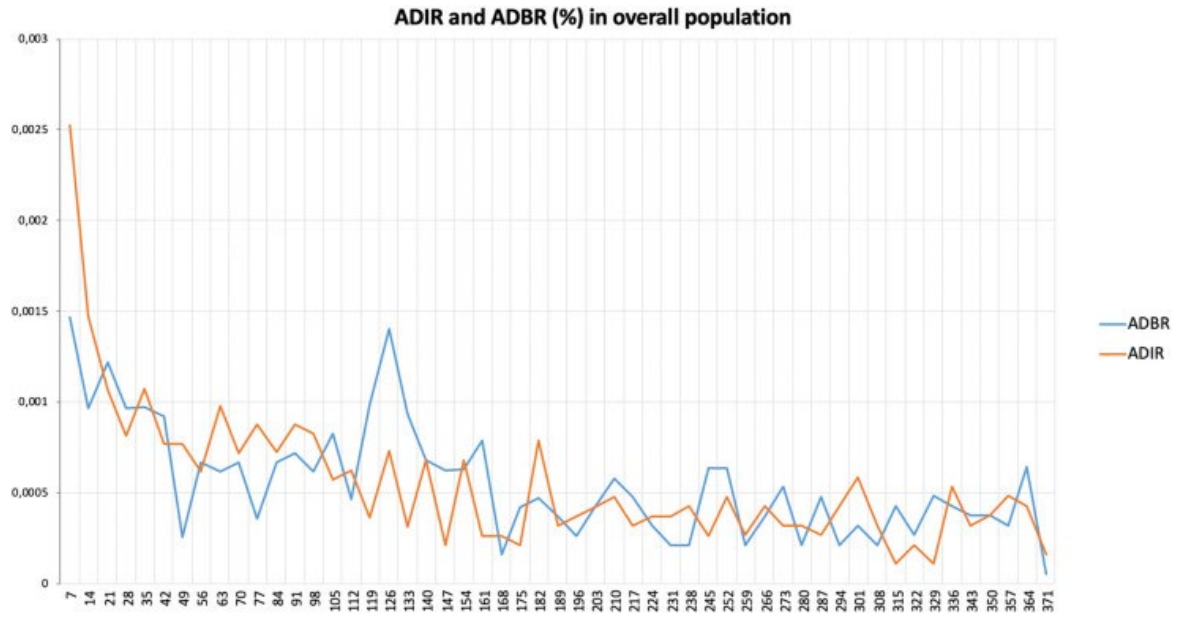

Figure 2. ADIR minus ADBR in the first year, subgroups.

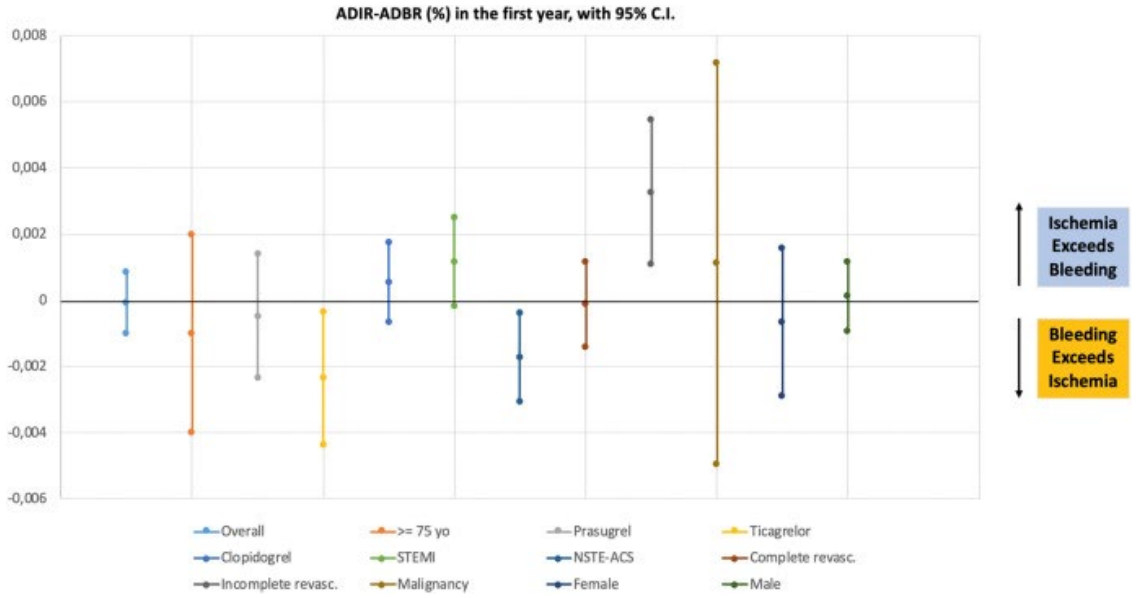

Figure 3. ADIR minus ADBR in the first month, subgroups.

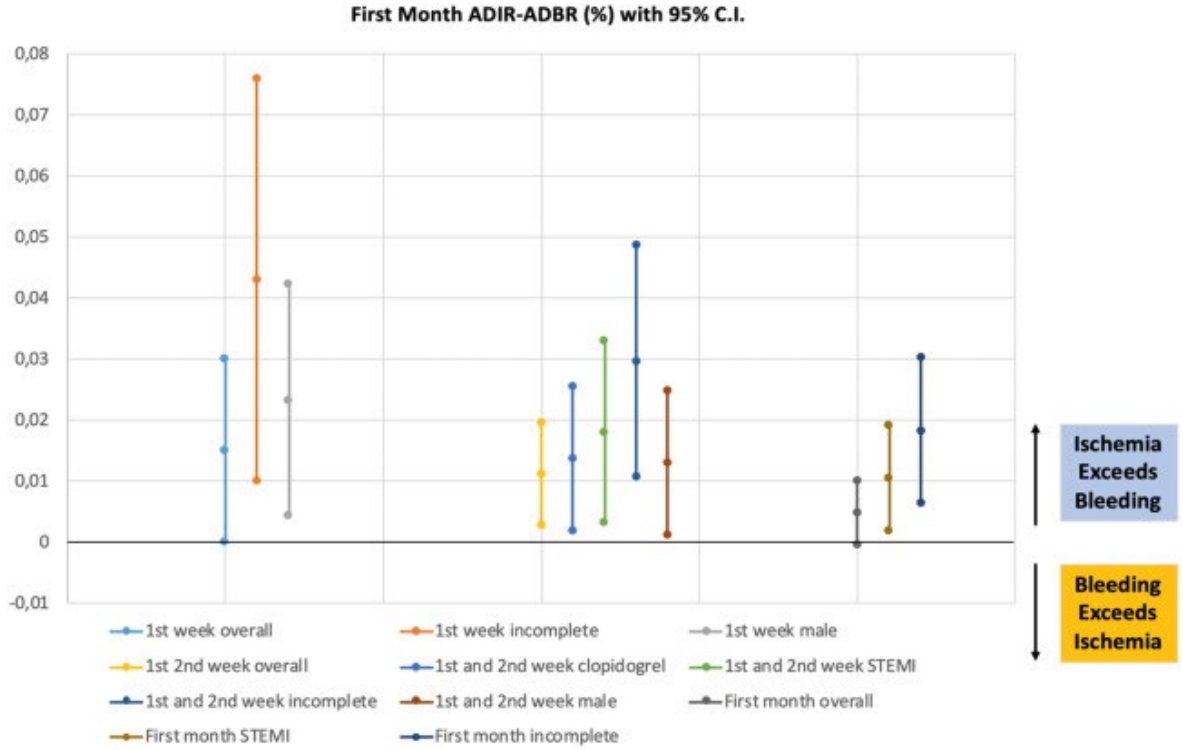

Figure 4. Monthly ADIR minus ADBR.